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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/670,626	09/25/2003	Xiaodong Wang	UTSD:1493	6739

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EXAMINER

WOLLENBERGER, LOUIS V

ART UNIT PAPER NUMBER

1635

DATE MAILED: 04/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/670,626

Applicant(s)

WANG ET AL.

Examiner

Louis V. Wollenberger

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 10 February 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-5 is/are pending in the application.
- 4a) Of the above claim(s) 5 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-4 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

Election/Restrictions

Applicants' timely election, with traverse, of Group I, drawn to methods of making siRNA, in the reply filed on February 10, 2006, is acknowledged.

The traversal is on the ground(s) that the searches required for the two groups will be the same as will be the examination issues.

Applicants' arguments have been fully considered but are not found persuasive. In the instant case, prior art searches of methods of making siRNA are not coextensive with prior art searches of kits and products used to make siRNA. Searching each of these inventions would require searching different keywords and keyword combinations related to each reagent in the kit and of each distinctive step of the method using divergent patent and non-patent literature databases. The different searches would then require subsequent in-depth analysis of the related and unrelated prior art literature to resolve issues of novelty, unobviousness, written description, and enablement with regard to both the method and the kit, placing a serious burden on the Office in terms of both search and examination. As such, it would be burdensome to perform a search and examination of inventions I and II together.

Accordingly, because these inventions are distinct for the reasons given in the previous Office Action, and the searches required for each are divergent and not coextensive, and because a search of Inventions I and II in a single application would present a serious burden on the examiner, restriction for examination purposes as indicated is proper.

The requirement is still deemed proper and is therefore made FINAL.

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The Examiner also wishes to clarify the previous Restriction Requirement, which inadvertently indicated that Group I included claims 1–5 and Group II included Claim 6. In fact the Application contains only 5 claims: Claims 1–4, drawn to methods of making siRNA; and Claim 5, drawn to a kit for making siRNA. In their response, Applicants have elected Group I, drawn to methods of making siRNA, which comprises Claims 1–4.

Status of the application

Claims 1–5 are pending. Claim 5 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1–4 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, complete or partial structure, physical and/or

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chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient.

Claim 1, the base claim, is drawn to a method of making siRNA, comprising recombinantly coexpressing a Dicer protein with an R2D2 protein to form a complex comprising the R2D2 protein and the Dicer protein, and contacting the complex with a target double-stranded RNA comprising a predetermined sequence under conditions wherein the complex cleaves the dsRNA into siRNA. Claim 2 limits claim 1 by stating that the R2D2 protein is a *Drosophila* R2D2 protein and the Dicer protein is a *Drosophila* Dicer-2 protein. Claims 3 and 4 further limit claims 1 and 2, respectively, by stating that the proteins are coexpressed in insect cells using a baculovirus expression system.

Thus, the claims are extremely broad. For example, in their broadest embodiments the claims include methods for making siRNA by recombinantly coexpressing any dicer protein with any R2D2 protein. That is, the instant methods encompass the use of recombinant dicer and R2D2 proteins, including any variants or isoforms thereof, from any organism. Similarly, although claim 2 is narrower in scope than claim 1, claim 2 encompasses any *Drosophila* R2D2 protein and any *Drosophila* dicer-2 protein.

Adequate written description does not exist in the instant application for all these methods. That is, the specification does not adequately allow persons of ordinary skill in the art

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to recognize that applicant(s) were in possession of the entire genus of R2D2 and dicer proteins needed to practice the entire genus of methods as now claimed in the instant claims.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed (pg. 1117). Because the level of skill and knowledge in the art increases over time, it is essential to determine possession as of the effective filing date.

In the instant case, the specification does not clearly allow persons of ordinary skill in the art to recognize that Applicants invented what is now claimed. The application does not enable the skilled artisan to clearly envision the detailed chemical structure of the encompassed genus of Dicer and R2D2 proteins, including all variants thereof, in all organisms.

An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

In the instant case, the claimed methods recite steps for recombinantly coexpressing two proteins referred to by name only: Dicer and R2D2. Applicants have not provided SEQ ID NO: identifiers for either the proteins themselves or for the polynucleotide sequences encoding these protein. However, a review of the instant application finds that R2D2 corresponds to the *Drosophila melanogaster* protein encoded by the sequence shown in GenBank Accession No. NM_135308 (page 3). (The Accession No. given on page 2 of the instant application appears to contain an additional "1".)

Accordingly, adequate written description is considered to exist for the R2D2 protein encoded by the mRNA sequence shown in GenBank Accession No. NM_135308, which sequence is considered to be constructively incorporated by reference. However, a recitation of this sequence in any claim would require the use of a SEQ ID NO: identifier corresponding to the sequence submitted to GenBank on or before the effective filing date of the instant application. Adequate written description does not exist for all other possible R2D2 proteins in all other species and organisms because Applicants have not demonstrated that, as of the effective filing date, they were in possession of all other R2D2 proteins from all organisms.

While Applicants state on page 3 that alternative species homologs are readily retrieved using conventional sequence algorithms and functionally confirmed using functional assays below, Applicants have not particularly defined what degree of homology is necessary and/or what domains or sequences, in particular, must be present in a protein or mRNA sequence for the protein to be positively identified as an R2D2 protein among the many other possible members of the family of dsRNA binding proteins for use in the instant method. For example, R2D2 (NM_135308) is said to bear 20.9% identity and 33.4% similarity to the *C. elegans* protein RDE-4 (page 5). Are Applicants, then, claiming a method for coexpressing RDE-4 with any dicer protein as well? Is RDE-4 to be considered an R2D2 protein, within the scope of claim 1, for example, for use in practicing the instantly claimed method? It is unclear.

Moreover, describing a protein on the basis of homology alone is considered to be unpredictable given that even a single amino acid substitution can disrupt or significantly alter a protein's activity (see, for example, Thornton et al., 2000, *Nature Struct. Biol.* 7 (Suppl.):991–

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994.) While Applicants state that R2D2 contains tandem dsRNA binding domains, it is unclear whether this feature alone is sufficient to describe all other R2D2 proteins.

Furthermore, while Applicants state that R2D2 proteins may be identified by functional assay (page 3), this does not help to describe the protein or proteins, but only invites trial and error screening without providing the skilled artisan with any distinguishable starting point. Additionally, while Applicants suggest on pages 4-5 that DCR-2 and R2D2/DCR-2 complexes may be identified by their "siRNA-generating activity," the particular conditions and steps for carrying out this assay, including the size, length, or sequence requirements, if any, of the dsRNA substrate are not clearly described in the specification or the prior art. Moreover, the particular conditions and requirements for the assay may vary from organism to organism. For example, Meister et al. state that for human recombinant Dicer, ATP-dependence of dsRNA processing has not been observed (pp. 343-4). In contrast, recombinant *Drosophila* Dicer-2 requires ATP (Meister et al., pp. 343-4).

Further, it is unclear what activity R2D2 protein has, if any, aside from the ability to bind dsRNA. In fact, the siRNA generating activity appears to be associated with DCR-2 not R2D2 (page 6, for example). R2D2 is said to be essential for binding to siRNA and for facilitating siRNA uptake by RISC (pages 1-2, 8). While a gel shift assay is described for detecting the presence of dsRNA binding proteins (page 7), this assay does not by itself distinguish R2D2 proteins from all other dsRNA proteins.

Accordingly, it appears as though R2D2 proteins are identified by a combination of methods, including siRNA-generating assays, immunoprecipitation, and mass spectrometry. Yet, Applicants have not described the materials (e.g., anti-R2D2 antibodies and anti-dicer

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antibodies) and methods needed to identify all possible R2D2 proteins in all organisms. Rather, Applicants merely invite the skilled artisan to experiment to find analogous proteins in other organisms.

Thus, while Applicants have adequately demonstrated possession of a method for making siRNA using the R2D2 protein encoded by NM_135308 from *Drosophila*, Applicants have not shown possession of all other possible R2D2 proteins in all other species because Applicants have not disclosed any specific structure/function relationship that would allow the skilled artisan to recognize and, thereby, recombinantly express all other possible R2D2 proteins as needed to practice the genus of methods now claimed.

Similarly, Applicants have not demonstrated possession of the genus of methods for recombinantly coexpressing any Dicer protein from any organism. In fact, a review of the instant application shows that Applicants' invention is directed specifically to the coexpression of *Drosophila* R2D2 (NM_135308) with *Drosophila* Dicer-2.

A review of the instant application and the post-filing art suggests that Applicants' contribution to the art is the characterization of a previously uncharacterized dsRNA binding protein, dubbed R2D2, which, in *Drosophila* cells, stably associates with Dicer-2, or DCR-2, which is said to be the principal siRNA-generating enzyme in *Drosophila* S2 cells (page 5 of the instant application; Liu et al., 2003 *Science* 301:1921-1925; Tomari et al., 2004 *Science* 306:1377-1380; Meister et al., 2004, *Nature* 431:343-349; Pellino et al., 2003, *Cell* 115(2):132-133). R2D2 is also said to be essential for RNAi in *Drosophila melanogaster* (page 6). Thus, the R2D2 protein described in the instant specifications is one that specifically associates with DCR-2 from *Drosophila*.

However, the particular features that set Dicer-2 apart from other proteins, including other Dicer proteins, are unclear. Applicants describe DCR-2 by name and function only and provide no readily identifiable structure or sequence showing one of skill in the art which sequence in particular is to be coexpressed with R2D2 (NM_135308). Again, as with R2D2, the Dicer proteins required for the instant methods are recited in terms of their function only, there is no art-recognized correlation between the structure and function, and the specification does not provide the support needed to enable one skilled in the art to predict with a reasonable degree of confidence the structure of the claimed Dicer proteins from a recitation of their function only.

Specifically, it cannot be readily ascertained from the instant application which Dicer protein(s) is/are to be coexpressed in the instant methods. No SEQ ID NO: identifiers or GenBank Accession numbers have been provided such that one of skill would be able to recognize the protein(s) that applicants are claiming for coexpression with R2D2. A review of the GenBank database indicates that DCR-2 corresponds to hundreds if not thousands of possible sequences. As a result, it is unclear what Dicer proteins are being claimed in the instant invention. What does *Drosophila* Dicer-2 look like, for example. Which cDNA sequence corresponds to Dicer-2? With regard to claim 2, for example, which particular Dicer cDNA sequence is to be coexpressed with R2D2 (NM_135308)?

Thus, applicants have not shown possession of the claimed methods using any and all possible Dicer proteins from all organisms. Rather Applicants invention is directed to a specific complex composed of two distinct *Drosophila* proteins designated R2D2, corresponding to NM_135308, and DCR-2, whose particular structural features, sequence, and characteristics are unclear.

MPEP §2163 states, in part: “[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when ... the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed. *In re Curtis*, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004).”

Accordingly, the instant claims are rejected for lack of written description support. While Applicants have described one R2D2 protein, Applicants have not demonstrated possession of all R2D2 proteins needed to practice the instant methods. While Applicants have shown that one R2D2 protein from *Drosophila* associates with one DCR-2 protein from *Drosophila*, the structure and or chemical nature of this DCR-2 protein (e.g., by SEQ ID NO: or by GenBank Accession No., or by a description of the full or partial sequence of DCR-2) has not been described, and no structure/function relationship has been set forth; thus it cannot be readily determined what Dicer protein is to be used in conjunction with the R2D2 protein in the instant invention.

Applicant is reminded that the written description requirement is separate and distinct from the enablement requirement. *In re Barker*, 559 F.2d 588, 194 USPQ 470 (CCPA 1977), cert. denied, 434 U.S. 1064 (1978); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991).

Claims 1–4 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention.

Factors to be considered in a determination of lack of enablement include, but are not limited to:

- (A) The breadth of the claims;
- (B) The nature of the invention;
- (C) The state of the prior art;
- (D) The level of one of ordinary skill;
- (E) The level of predictability in the art;
- (F) The amount of direction provided by the inventor;
- (G) The existence of working examples; and
- (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

The claims are described above.

The invention is in a class of invention that the CAFC has characterized as “the unpredictable arts such as chemistry and biology.” *Mycogen Plant Sci., Inc. v Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The claims are very broad. For instance, in their broadest embodiments, the claims encompass methods for making siRNA comprising recombinantly coexpressing any Dicer

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protein with any R2D2 protein from any species or organism to form a complex, and contacting the complex with dsRNA, wherein the dsRNA is cleaved into siRNA. Thus, to enable the instantly claimed methods, the specification must teach one of skill in the art how to make the constructs for recombinantly coexpressing all possible Dicer and R2D2 proteins. However, as explained above, the specification fails to describe the sequences needed to practice the entire genus of methods now claimed. That is, the specification does not teach the skilled artisan how to make the entire genus of recombinant proteins, including all possible Dicer and R2D2 proteins, required for practicing the entire genus of methods for making siRNA.

A review of the instant application finds working examples and disclosure directed to the use of two *Drosophila* proteins, designated Dicer-2 and R2D2, which are said to cooperate as a complex to cleave long dsRNA into short interfering RNA, or siRNA. Further, the complex is said to facilitate siRNA uptake by RISC, which is essential for RNAi in *Drosophila* cells.

While *Drosophila* R2D2 protein is readily identified as the protein encoded by NM_135308, other R2D2 sequences have not been set forth, nor has adequate guidance been given teaching one of skill how to identify, isolate, clone, and express all other conceivable R2D2 proteins in the claimed genus. Furthermore, while Applicants teach that R2D2 cooperates with Dicer-2 from *Drosophila*, and while it appears as though Dicer-2 has been previously characterized in the prior art (Bernstein et al., 2001, *Nature* 409:363-6, for example), it is, nevertheless, unclear which Dicer sequence in particular is intended for recombinant coexpression with R2D2 in the instant claims, since the prior art and sequence databases are replete with teachings of various Dicer proteins and sequences from *Drosophila* and other organisms. For example, Meister et al. teach that *Drosophila* has two paralogues, Dicer-1 and

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Dicer-2, which function in miRNA and dsRNA processing pathways (page 343). Four Dicer-like proteins have been identified in *Arabidopsis thaliana* (Meister et al., page 344). Which sequences of the many now disclosed for different organisms is/are suitable for coexpression with which R2D2 proteins to practice the claimed invention? While describe one Dicer/R2D2 complex for making siRNA, applicants do not describe every Dicer/R2D2 complex such that the skilled artisan could recombinantly coexpress and make every complex, as now required.

Considering the breadth of the claims, the state of the art at the time of filing, the level of unpredictability in the art, and the limited guidance and working examples provided by the instant application, the Examiner submits that the skilled artisan would be required to conduct undue, trial and error experimentation to practice the claimed invention commensurate with the claims scope.

Accordingly, the instant claims are rejected for failing to comply with the enablement requirement.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis V. Wollenberger whose telephone number is 571-272-8144. The examiner can normally be reached on Mon–Fri, 8:00 am–4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval system (PAIR). Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

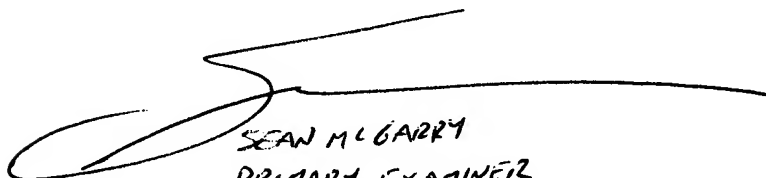
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March 20, 2006



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